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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,847	12/12/2000	C. Frank Bennett	ISPH-0524	4732

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,847	BENNETT ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-16 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-16 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Response to Arguments

2. Applicant's arguments with respect to claims 1-3, 6-13, 21-26, and 31-32 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, 6-11 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 95/04748 A1) in view of Buchardt et al. (US 6,395,474 B1).

Anderson et al. disclose peptide nucleic acid (PNA) oligomers targeting the mRNA sequences that are known to control mRNA stability, processing, and/or translational efficiency (see page 26, lines 9-11). Anderson et al. specifically disclose PNA oligomers targeted to the 5' CAP, intron/exon junction sequences, and the 5' UTR of mRNA encoding the immediate early messenger RNAs of cytomegalovirus (IE mRNAs; see page 25-26).

Anderson et al. does not specifically disclose PNA oligomers comprising either lysine or arginine at the C-terminus used in a method for modulating splicing of a wild-type mRNA target. Additionally, Anderson et al. does not disclose wherein modulation of splicing results in an

altered ration of splice products, redirection of splicing, an altered ratio of splice products, exclusion of one more exons.

Buchardt et al. (US 6,395,474 B1) teach that the binding characteristics of PNA may be modulated by attaching ligands at either terminus of the PNA, representative ligands include basic groups such as lysine or polylysine. These modifications will strengthen the binding of PNA due to electrostatic interaction (see col. 10, lines 20-28). Buchardt et al. teach that PNA may be used as an antisense-type moiety (see col. 10, lines 48-50) to target mRNA such that binding of the PNA to the target hinders the action of ribosomes and consequently the translation of the mRNA into protein (col. 11, lines 18-21).

It would have been obvious at the time the invention was made to modify the teachings of Anderson et al. with the modifications taught by Buchardt et al. to design the method of the instant invention. One of ordinary skill in the art would have been motivated to modify the PNA oligomers targeting to the intron/exon junctions of IE pre-mRNAs disclosed in Anderson et al. with the terminal lysine modifications taught by Buchardt et al., because this modification is disclosed as having the ability to strengthen the binding of PNA oligomers to its target nucleic acid. Moreover, although Anderson et al. does not explicitly teach a method for modulating splicing of an mRNA target, however, absent evidence to the contrary, because the PNA oligomers of Anderson et al. include those that are designed to bind at the intron/exon junctions of a non-mutant form of the IE mRNAs, one of ordinary skill in the art would have expected that these PNA oligomers, would function to modulate splicing. Additionally, although Anderson et al. does not teach that by designing antisense compounds to target intron/exon junctions, splicing will be modulated by producing an altered ratio of splice products, redirection of splicing, or

resulting in the exclusion of one more exons, one of skill in the art would have recognized that these results are all consequences of disrupting the normal splicing machinery in a cell by antisense blockage of the intron/exon junctions within a wild-type mRNA target.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4-16, and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed method *in vitro*, does not reasonably provide enablement for practicing the claimed method *in vivo* for therapeutic treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The instant claims are directed to a method of controlling the behavior of a cell through modulation of the processing of a selected wild-type mRNA target, wherein said processing may encompass splicing, polyadenylation, or regulating the stability of an mRNA target. The instant claims encompass controlling an undefined behavior of a cell by modulating the processing of an

undefined mRNA target. The specification as filed does not provide a sufficient description of the wild-type mRNA targets encompassed by the instant claims such that the particular cellular behavior to be controlled in the claimed methods would be apparent to the skilled artisan. Applicants do not provide a clear nexus between the cellular behavior to be controlled and the particular mode of modulation of processing of the wild-type mRNA target to be administered, nor is there a clear nexus between the structure of the wild-type mRNA or the antisense compound used in the claimed method and the corresponding cellular behavior to be modulated.

The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets *in vivo*, and the structures of the modified antisense oligonucleotides, modes of delivery in a *in vivo* such that the processing of said mRNA target is modulated at a significant level and for a sufficient amount of time to control a particular cellular behavior, and further wherein said cellular behavior is a desired therapeutic effect in an animal. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully treat an animal having a disease or condition associated the expression of an undefined wild-type mRNA target comprising the administration of the modified antisense compounds of the present invention. The specification as filed provides only *in vitro* data regarding the ability of antisense treated cells to modulate mRNA processing of human bcl-x, E-

selectin, and IL-5 receptor α mRNA, wherein said processing was associated with the modulation of polyadenylation and splicing, and further wherein modulation of splicing resulted in the control of apoptosis or cellular proliferation *in vitro* (see pages 72-110). However, the examples do not provide any clear nexus between the in vitro results observed by Applicants and the administration of the claimed method for therapeutic purposes.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998: See IDS: AB), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influence the activity of antisense-based compounds. Specifically, Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors, including, for example: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. Non-antisense effects, such as non-specific antisense binding to proteins, have the potential to influence cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors,

which influence the behavior of antisense based compounds thereby rendering the activity of these compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Moreover, Branch states that "[H]owever, their *(antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells*, Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics is generally unpredictable and those highly skilled in the art are currently working

towards making antisense therapy more predictable, although there are many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability known to be associated with the antisense art at the time the invention was made.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the processing of a single mRNA target is modulated and the desired secondary treatment effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Notice of References Cited

7. Only the Jen et al. and Anderson et al. references will be forwarded to Applicants, all other references cited in this action were previously forwarded to Applicants during the prosecution of Application 09/277,020 or are US Patent documents.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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